REMARKS

Applicants have carefully studied the Final Office Action mailed on May 17, 2005, which issued in connection with this application. Applicants gratefully acknowledge the courtesy shown by Examiner Tracy Vivlemore and the Examiner's Supervisor, Andrew Wang, in providing recommendations for response to the present Office Action and in considering a proposed amendment to the claims (same as above) in a telephonic interview with applicants' representatives, S. Peter Ludwig and Irina Vainberg, on August 15, 2005. The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Applicants' Statement of the Substance of the Telephonic Interview with Examiners Wang and Vivlemore

In the telephonic interview on August 15, 2005, applicants' representatives, S. Peter Ludwig and Irina Vainberg, addressed 35 U.S.C. §112, second paragraph, rejection raised by the Examiner in connection with the use of the terms "bcl-2 mRNA" and "bcl-2 primary transcript" in claims 70 and 72-74. In particular, applicants' representatives addressed the Examiner's concern that the use of the term "mRNA" to refer to transcripts that have undergone splicing does not find clear support in the '692 priority application. Specifically, applicants' representatives pointed out that (i) both the present application and the '692 priority application disclose TI-AS antisence oligonucleotide which is directed against the bcl-2 translation initiation site and contains sequences complementary to the first four codons and "a portion" of the 5' untranslated region (5'-UTR) of the "mature" bcl-2 mRNA and (ii) as disclosed in the experimental example on pages 28-30 of the '692 priority application, TI-AS oligonucleotide successfully inhibited proliferation of NIH 3T3 cells stably transfected with bcl-2 cDNA expression constructs, which produce only "mature" bcl-2 mRNA. It was agreed to by the Examiners that this disclosure demonstrates that TI-AS anticode oligomer is complementary to the processed "mature" mRNA.

Examiners Vivlemore and Wang have then considered applicants' suggested amendment to the claims (identical to the amendment provided in the present response), in which, to avoid any ambiguity with respect to the meaning of the term "mRNA", claims 70 and 72-74 have been amended to recite only the term "mRNA". The Examiners indicated that they would be willing to allow claims as amended.

The Examiners also agreed with the applicants' interpretation of the term "mRNA" in the claims as amended, *i.e.*, that the term "mRNA" recited in the claims as amended encompasses both primary transcripts (pre-mRNA) and processed "mature" transcripts. It was agreed to by the Examiners that the applicants would make a statement to this effect in the response to the Office Action.

In closing, applicants' representatives also noted that a Terminal Disclaimer will be filed to overcome the obviousness-type double patenting rejection. In response, the Examiners noted that, in light of the proposed amendment and Terminal Disclaimer, there are no remaining issues in the case.

The present amendments and remarks address all substantive issues discussed during the telephonic interview of August 15, 2005 and are intended to be fully responsive to all points of rejection raised by the Examiner. These amendments and remarks are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 53, 70 and 72-88 are pending and at issue in the application. Claims 53 and 76-81 have been allowed. Claims 70, and 72-74 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 70, 72, 73, 75, and 82 have been rejected under the judicially created doctrine of obviousness-type double patenting. Claims 83-88 have been objected to as being dependent upon a rejected base claim.

Claim 70 has been amended by deleting the recitation "or a portion of a human bcl-2 primary transcript". Similarly, claim 74 has been amended by deleting the recitation "or a human bcl-2 primary transcript". Claims 72 and 73 have been amended by replacing the recitation "primary transcript" with the recitation "mRNA".

The above-identified amendments have been introduced to expedite the prosecution and to remove any ambiguity with respect to the meaning of the term "mRNA" as recited in the present claims. As agreed to by the Examiner and her supervisor during the telephonic interview of August 15, 2005, the term "mRNA" recited in the claims as amended encompasses both primary transcripts (pre-mRNA) as well as processed "mature" transcripts. It follows that the use of the term "primary transcript" is repetitive to the use of the term "mRNA". By the present amendment, the term "primary transcript" has been deleted to eliminate the repetitiveness. As agreed to by the Examiner and her supervisor during the telephonic interview of August 15, 2005, claims as amended encompass (i) anticode oligomers which are complementary to bcl-2 primary transcripts (pre-mRNA) (or a portion thereof) and (ii) anticode oligomers which are complementary processed "mature" bcl-2 transcripts (or a portion thereof).

No new subject matter has been added as a result of these amendments, no new search is required, and no new issues are raised.

35 U.S.C. §112, Second Paragraph Rejections

In the Office Action, the Examiner has rejected claims 70 and 72-74 under 35 U.S.C. §112, second paragraph, as being indefinite for failing particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection revolves around the use of the terms "bcl-2 mRNA" and "bcl-2 primary transcript". In the Office Action, the Examiner contends that the use of these terms makes claims 70 and 72-74 indefinite and suggests replacing these terms with the single generic term "mRNA", because, in the Examiner's opinion, the use of the term "mRNA" to refer to transcripts that have

undergone splicing does not find clear support in the priority application Ser. No. 07/288,692 (the '692 application) and is taught away from by the disclosure of anticode oligomers which are complementary to splice donor or splice acceptor site.

In response, applicants respectfully note that the present specification uses the term "pre-mRNA" or "primary transcript" and the '692 priority specification uses the term "primary transcript" to refer to the bcl-2 primary transcript (see, *e.g.*, page 3, lines 17-20; page 12, lines 8-12 and lines 24-29, and page 21, lines 1-4 of the present specification and page 17, lines 5-8 of the '692 priority specification). The term "mRNA" as recited in the present specification and in the priority '692 specification is either used to encompass both primary and "mature" transcripts (see, *e.g.*, page 4, line 6; page 5, lines 9 and 18; page 7, line 17 of the '692 priority specification and page 13, line 16 of the present specification) or, in several instances, is used more narrowly to encompass only processed "mature" transcripts (see, *e.g.*, page 28, line 23 of the '692 priority specification and page 3, line 20; page 12, lines 11 and 26 of the present specification). This probably lead to the Examiner's confusion.

To avoid any ambiguity with respect to the meaning of the term "mRNA" as recited in the present claims, claims 70 and 72-74 have been amended to recite only the term "mRNA". Specifically, claim 70 has been amended by deleting the recitation "or a portion of a human bcl-2 primary transcript", claim 74 has been amended by deleting the recitation "or a human bcl-2 primary transcript", and claims 72 and 73 have been amended by replacing the recitation "primary transcript" with the recitation "mRNA". As agreed to by the Examiner and her supervisor during the telephonic interview of August 15, 2005, the term "mRNA" recited in the claims as amended encompasses both primary transcripts (pre-mRNA) as well as processed "mature" transcripts. It follows that the use of the term "primary transcript" is repetitive to the use of the term "mRNA". By the present amendment, the term "primary transcript" has been deleted to eliminate the repetitiveness. As agreed to by the Examiner and her supervisor during the telephonic interview of August 15, 2005, claims as amended encompass (i) anticode oligomers which are complementary to bcl-2 primary transcripts (pre-mRNA) (or a portion thereof) and (ii) anticode oligomers which are complementary to processed "mature" bcl-2 transcripts (or a portion thereof).

In the Office Action (paragraph bridging pages 2 and 3), the Examiner argues that the use of the term "mRNA" to refer to transcripts that have undergone splicing does not find clear support in the '692 priority application and is taught away from by the disclosure of anticode oligomers which are complementary to splice donor or splice acceptor site.

Applicants respectfully disagree with this reasoning and note that, in contrast to the Examiner's assertion, the disclosure of anticode oligomers directed against splice donor site and splice acceptor site does not constitute any teaching away with respect to the processed "mature" mRNA but simply constitutes several select examples out of many different examples of anticode oligomers provided in the application (see, *e.g.*, page 4, lines 4-9; page 4, line 19 - page 6, line 2, and page 7, line 15 - page 8, line 1 of the '692 priority application and page 3, lines 17-22; page 4, line 1 - page 5, line 4; page 10, lines 3-6, and page 12, lines 1-16 of the present application).

In contrast to the Examiner's assertion, in addition to disclosing the use of anticode oligomers which are complementary to the bcl-2 primary transcript (pre-mRNA) (such as, *e.g.*, SD-AS oligonucleotide directed against splice donor site and SA-AS oligonucleotide directed against splice acceptor site as shown in Table 1), both the present application and the '692 priority application disclose anticode oligomers which are complementary to the processed "mature" mRNA. Indeed, as generally stated at page 7, lines 15-19 of the '692 priority application (or page 12, lines 1-5 of the present application), "[t]he oligodeoxynucleotides are preferably selected from those oligodeoxynucleotides complementary to strategic sites along the mRNA of bcl-2, such as the translation initiation site, donor and acceptor splicing sites, or sites for transportation or degradation". Out of the named types of strategic sites, at least translation initiation site and degradation sites are always present in the processed "mature" mRNA.

For example, both the present application and the '692 priority application disclose TI-AS antisence oligonucleotide which is directed against the bcl-2 translation initiation site and contains sequences complementary to the first four codons and "a portion" of the 5' untranslated region (5'-UTR) of the "mature" bcl-2 mRNA (see, *e.g.*, Table 1 and page 4, lines 4-9; page 4, line 19 - page 5, line 3; page 5, line 24 - page 6, line 2, and page 7, lines 15-24 of the '692 priority application as

well as Table 1 and page 3, lines 17-22; page 4, lines 1-15; page 10, lines 3-6, and page 12, lines 1-16 of the present application). As disclosed in the experimental example on page 14, lines 16-21 and pages 28-30 of the '692 priority application (or page 18, lines 3-9 and Example 11 on pages 30-33 of the present application), TI-AS oligonucleotide successfully inhibited proliferation of NIH 3T3 cells stably transfected with bcl-2 cDNA expression constructs. As these bcl-2 cDNA expression constructs contain cDNA[1], they produce only "mature" bcl-2 mRNA. As agreed to by the Examiner and her supervisor during the telephonic interview of August 15, 2005, this disclosure demonstrates that TI-AS anticode oligomer is complementary to the processed "mature" mRNA.

The importance of producing anticode oligomers both to primary bcl-2 transcripts (pre-mRNA) and to processed mRNA is further emphasized by the disclosure that bcl-2 gene gives rise to several different transcripts through alternative splice cite selections and to one minor transcript (encoding 22 kDa bcl-2-beta) which does not undergo splicing (see, *e.g.*, page 17, lines 10-17 of the '692 priority application and page 5, lines 1-4; page 21, lines 6-13 of the present application).

In light of the above-presented arguments and amendments, it is believed that the indefiniteness rejection has been overcome and withdrawal of such is respectfully requested.

Obviousness-Type Double Patenting Rejection

In the Office Action, claims 70, 72, 73, and 75 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 16 and 18 of U.S. Patent No. 6,841,541. The Examiner has further rejected claims 70, 73 and 82 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5 of U.S. Patent No. 5,734,033.

[1] It is well established in the art that cDNA represents a DNA copy of the processed "mature" mRNA sequence, which unlike genomic DNA lacks intron sequences (see, *e.g.*, illustration provided in Figure 8-35 of *Molecular Biology of the Cell*, 4th ed., Alberts *et al.* eds., New York: Garland Publishing; 2002; attached as Exhibit B).

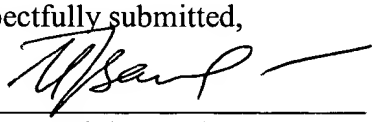
In response, applicants hereby submit a Terminal Disclaimer (attached as Exhibit A). Reconsideration and withdrawal of the double patenting rejections is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 53, 70 and 72-88 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Dated: August 26, 2005

Respectfully submitted,

By 

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